

Janssen EMEA \*

## Statistical Analysis Plan – Main analysis Week 48

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**Study of Treat to Target Versus Routine Care Maintenance Strategies in Crohn's Disease  
Patients Treated with Ustekinumab****STARDUST**

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**Protocol CNTO1275CRD3005; Phase 3b****CNTO1275 (ustekinumab)**

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**Compliance:** The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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**AMENDMENT HISTORY**

Not applicable.

**ABBREVIATIONS**

<b>Abbreviation</b>	<b>Text</b>
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BWT	bowel wall thickness
CDAI	Crohn's Disease Activity Index
CDAI-70	70-point improvement versus baseline in Crohn's Disease Activity Index
CI	Confidence interval
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical Study Report
CT	computed tomography
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECCO	European Crohn's and Colitis Organisation
eCRF	Electronic case report form
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
EU	European Union
EQ-5D-5L	EuroQoL-5D-5L Health Questionnaire
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FC	Fecal calprotectin
FDA	Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IUS	high-frequency intestinal ultrasound
IV	Intravenous
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PD	Pharmacodynamic
PI	Principal investigator
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome(s)
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SES-CD	Simple endoscopic score for Crohn's disease
SmPC	Summary of Product Characteristics
TB	Tuberculosis
TNF	tumor necrosis factor
WHO-DD	World Health Organization Drug Dictionary
WPAI	Work Productivity and Activity Impairment

## 1. INTRODUCTION

In this trial, after a screening period of up to 5 weeks, eligibility of subjects will be evaluated, and all eligible subjects will initiate intravenous (IV) induction treatment with ustekinumab followed by a 90 mg SC injection of ustekinumab at week 8. At Week 16, subjects who do not achieve a CDAI improvement of 70 points versus Week 0 will leave the study. Subjects who remain in the study will be randomized in a 1:1 ratio to either one of two arms for open-label maintenance treatment up to Week 48: the treat to target arm or the routine care arm.

Within this study an exploratory ultrasound substudy is started with the aim to collect high-frequency intestinal ultrasound (IUS) parameters to assess changes in IUS parameters indicating transmural response to treatment with ustekinumab up to week 48. Participation in this substudy is optional for subjects participating in the main study.

From Week 48, subjects will continue ustekinumab treatment in the study extension period, up to Week 104. The frequency of dosing will be based on endoscopic and/or clinical remission at Week 48, and subsequently on clinical remission and biomarker findings.

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the main analysis of the first 48 weeks. The main population will consist of all subjects enrolled in the study who receive at least one study treatment and who are randomized to T2T or RC arm. Results will be presented per treatment arm. Subject characteristics, efficacy and safety endpoints will be included in this main analysis.

Subject characteristics, based on subjects who participated in substudy, and all IUS parameters assessed during the first 48 weeks of the study will also be included in this main analysis.

### 1.1. Trial Objectives

The primary objective is to evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving endoscopic response.

Secondary objectives are:

- To examine the robustness of the primary endpoint analysis, sensitivity analyses of the primary endpoint will be conducted.
- To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving endoscopic remission, mucosal healing, clinical remission and clinical response.
- To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in eliminating the need for corticosteroids while maintaining disease control.
- To evaluate the effect of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach on serum CRP and FC levels and on health-related quality of life (QoL), patient-reported outcomes (PROs) and pharmacoeconomics.
- To describe the safety of two SC ustekinumab maintenance regimens in a randomized population.

Exploratory objectives within the substudy are to explore:

- the effectiveness of ustekinumab treatment in achieving IUS response.

- the effectiveness of ustekinumab treatment in achieving IUS remission.
- the effect of ustekinumab treatment on BWT.
- the effect of ustekinumab treatment on vascularization as determined by color Doppler signal.
- the effect of ustekinumab treatment on loss of bowel wall stratification.
- the effect of ustekinumab treatment on inflammatory mesenteric fat.

## 1.2. Trial Design

This is a randomized, open-label, parallel-group, multicenter, multinational, Phase 3b interventional study of ustekinumab in adult subjects with active moderate to severe Crohn's disease. A target of 650 adult male and female subjects with endoscopic evidence of active disease will be enrolled.

During a screening period of up to 5 weeks, eligibility of subjects will be evaluated, and centrally-read endoscopic assessments at screening will be used for baseline evaluation. At Week 0, all eligible subjects will initiate IV induction treatment with ustekinumab, in line with the EU SmPC, on a weight-tiered basis at a dose of approximately 6 mg/kg IV. At Week 8, all subjects will receive a 90 mg SC injection of ustekinumab.

At Week 16, subjects who do not achieve a CDAI improvement of 70 points versus Week 0 will leave the study. Subjects who remain in the study will be randomized in a 1:1 ratio to either one of two arms for open-label maintenance treatment up to Week 48: the treat to target arm or the routine care arm.

Subjects randomized to the **routine care arm** will receive an ustekinumab maintenance dosing regimen consistent with the EU SmPC.

Maintenance treatment in the **treat to target arm** will also involve initial assignment to 12 weekly or 8 weekly 90 mg SC treatment, which in this arm will be based on endoscopic results at Week 16. However, within the treat to target approach, there is the potential for more intensive management, with optimization to 4 weekly dosing for subjects failing to meet treatment targets following 8 weekly dosing. Treatment targets are based on CDAI and biomarkers (CRP and FC).

The main study treatment period is 48 weeks, of which 32 weeks will be the randomized maintenance treatment period. Subjects completing the study will receive between 3 and 7 maintenance treatment doses of study drug, depending on the treatment arm and adjustments to dosing frequency.

From Week 48, subjects will continue ustekinumab treatment in the study extension period, up to Week 104. The frequency of dosing will be based on endoscopic and/or clinical remission at Week 48, and subsequently on clinical remission and biomarker findings.

All subjects will have a final safety follow-up visit 16 weeks after the last administration of ustekinumab within the study.

## 1.3. Statistical Hypotheses for Trial Objectives

The hypothesis is that a 'treat to target' ustekinumab maintenance treatment strategy coupled with early endoscopic assessment will result in a higher endoscopic response rate (defined as the percentage of subjects achieving  $\geq 50\%$  reduction in SES-CD versus baseline) after 48 weeks of treatment, compared with a pragmatic (per EU SmPC) maintenance treatment strategy in subjects with Crohn's disease. This study is designed to show that the percentage of subjects with endoscopic response at Week 48 in the

treat to target arm is 15% higher compared with the routine care arm: endoscopic response in the routine care arm is estimated at 30% of subjects, in the treat to target arm is estimated at 45% of subjects.

The primary endpoint of this study is endoscopic response at Week 48 of the study. Endoscopic response is defined as showing (yes or no) a reduction from baseline in the SES-CD score of  $\geq 50\%$ . The null hypothesis that is to be tested to address the primary objective of the trial is that there is no difference between the routine care and treat to target arm in the primary efficacy endpoint.

#### 1.4. Sample Size Justification

A Fisher's exact test with a 0.050 two-sided significance level will have 80% power to detect the difference between the routine care arm proportion of 30% and the treat to target arm proportion of 45% when the sample size in each group is 174. With an estimated CDAI 70 response at Week 16 between 65% and 70%, and a dropout rate between 10% and 17.5%, a total of 650 subjects should be enrolled.

#### 1.5. Randomization and Blinding

As this is an open study, blinding procedures are not applicable.

At Week 16, subjects achieving CDAI improvement of  $\geq 70$  points versus baseline (Week 0), will be randomized in a 1:1 ratio to one of two ustekinumab maintenance treatment arms: the treat to target arm or the routine care arm. Central randomization will be implemented in this study. Subjects will be randomly assigned to one of two treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by whether the subject was biologic naïve at baseline or had prior exposure to 1 biologic for treatment of Crohn's disease, and according to baseline SES CD score  $\leq 16$  or SES CD  $> 16$ .

## 2. GENERAL ANALYSIS DEFINITIONS

### 2.1. Visit Windows

Unless otherwise specified, actual scheduled visits will be used for over time summaries and listings, with no visit windows applied.

**Only for endpoint:** As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign the early termination visits to an analysis visit. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1. If a subject has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses, but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 1) are the visit windows and the target days for visit week 16 and week 48 that should be used to reschedule an early termination visit.

**Table 1 – Visit Windows**

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
1	Screening	< 1	-14 to 1



2	Baseline <sup>a</sup>	<=1	1
3	Week 8	44-85	57
4	Week 16 <sup>b</sup>	86-141	113
5	Week 48	306-377 <sup>c</sup>	336

\* Relative to Study Day 1

a First medication day is Day 1 (baseline – week 0).

b Randomization is at Week 16

c Window is based on actual week 48 visits

## 2.2. Pooling Algorithm for Analysis Centers

Not applicable.

## 2.3. Analysis Sets

### 2.3.1. All Enrolled Analysis Set

The all enrolled analysis set includes all subjects who were not screen failures or did not drop out during screening.

### 2.3.2. Full Analysis Set

The full analysis set (FAS) includes all enrolled subjects who received at least 1 dose of study agent.

### 2.3.3. Full Randomized Analysis Set

The all full analysis set (FRAS) includes all subjects from FAS that were randomized at week 16, regardless of study treatment being administered once randomized. Data of the first 16 weeks of induction for all subjects in FAS was analyzed as an interim analysis (see section 3).

### 2.3.4. Efficacy Analysis Set(s)

The Efficacy analysis set includes all subjects from FRAS.

### 2.3.5. Per-Protocol Analysis Set(s)

The per protocol analysis set (PP) includes the subjects in the full analysis set (FAS) who are in compliance with the protocol.

### 2.3.6. Safety Analysis Set

The safety analysis set includes all subjects from FRAS.

### 2.3.7. IUS All enrolled Analysis Set

The IUS all enrolled analysis set includes all subjects from the FAS that participated in the CNTO1275CRD3005 substudy. That is, signed ICF for substudy and at least one IUS assessment has been performed.

### 2.3.8. IUS Efficacy Analysis Set

The IUS efficacy analysis set (IUS FRAS) includes all subjects from FRAS that participated in the CNTO1275CRD3005 IUS substudy with most affected part of the bowel available at baseline.

### 2.3.9. Pharmacokinetics Analysis Set

The PK Analysis Set is defined as subjects from FAS that have at least 1 valid blood sample drawn for PK analysis.

## 2.4. Definition of Subgroups

TBD

## 2.5. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is  $\geq$  date of Day 1
- Visit date - date of Day 1, if visit date  $<$  date of Day 1

There is no 'Day 0'.

## 2.6. Baseline and Endpoint

Baseline is defined as the last observation prior to the start of the first study agent administration. Date and time of baseline assessment can be the same as date and time of first study agent administration (for example for blood pressure assessments) provided the time point of assessment is referred to as 'prior to infusion'.

Endpoint is defined as the last available postbaseline result within the main analysis period (i.e. first 48 weeks of the study). Unscheduled visit results are included in this definition and will be considered as the endpoint value if the unscheduled visit result is the last postbaseline result available within the analysis period.

## 2.7. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start
  - The day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - The day of study agent start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date
  - Month and day of the study agent start date, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study agent start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

### 3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An Interim Analysis has been performed on all subjects that received at least one study medication and either completed the week 16 period or discontinued the study prior to week 16. A separate SAP has been developed for this interim analysis (See attachment 1)

### 4. SUBJECT INFORMATION

Descriptive statistics (mean, standard deviation (SD), median, inter quartile (IQ) range, 95% confidence interval (CI), minimum and maximum) will be provided for continuous variables. Counts, percentages and 95% CI intervals will be provided for categorical variables. No formal statistical analyses for treatment group comparisons will be performed. All results in this section will be based on the Full Analysis Set and will be reported both overall, as well as per treatment group, unless otherwise specified.

#### 4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristic variables will be descriptively summarized by randomized treatment groups and overall. No formal statistical comparison is planned. P-values will not be provided.

##### 4.1.1. Demographics

Table 2 presents a list of the demographic variables that will be summarized. Demographic data will also be analyzed for the IUS Full Analysis Set.

**Table 2: Demographic Variables**

<b>Continuous Variables:</b>	<b>Summary Type</b>
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median, 95% CI and range [minimum and maximum])
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m <sup>2</sup> )	
Temperature (°C)	
Pulse (beats/min)	
Systolic Blood Pressure (mmHg)	
Diastolic Blood Pressure (mmHg)	
<b>Categorical Variables:</b>	Frequency distribution with the number and percentage of subjects in each category.
Age (18-25 years, 26-50 years, 51-64 years, and ≥65 years)	
Sex (male, female)	
BMI (underweight <18.5 kg/m <sup>2</sup> , normal 18.5-<25 kg/m <sup>2</sup> , overweight 25-<30 kg/m <sup>2</sup> , obese ≥30 kg/m <sup>2</sup> )	

#### 4.1.2. Baseline Characteristics

Table 3 presents a list of the baseline disease characteristics that will be summarized.

**Table 3:** Baseline Disease Characteristics

Continuous Variables:	Summary Type
Time from diagnosis to first study agent administration (months)	Descriptive statistics (N, mean, standard deviation [SD], median, 95% CI and range [minimum and maximum])
CDAI	
Hematocrit (%)	
SES-CD	
IBDQ total score	
EQ-5D-5L VAS, Index score and levels of each of the 5 dimensions, i.e. mobility, self-care, usual activities, pain/discomfort and anxiety/depression	
FACIT-F	
HADS-A and HADS-D subscale scores for anxiety and depression	
Time lost from work	
WPAI for absenteeism, presenteeism, work productivity loss, and activity impairment.	
CRP	
FC	
<b>Categorical Variables:</b>	Frequency distribution with the number and percentage of subjects in each category.
Location of disease (Ileal, Colonic, Ileocolonic, N/A)	
ECG method (6 Lead Standard, 10 Lead Standard, 12 Lead Standard)	
ECG Overall Interpretation (Normal, Abnormal, Not Evaluable)	
Is ECG Abnormal Interpretation Clinically significant (Yes, No)	
What was Subject's Previous Experience with Tuberculosis (History of Tuberculosis, Occupational exposure to individuals with active TB, Personal exposure to individuals with active TB, None)	
Tuberculosis Chest Radiograph Result (Normal; Abnormal, no suspicion of TB; Abnormal, suspicion of TB)	
TB assessment performed (Quantiferon TB Gold In-Tube test; Tuberculin skin test)	
Quantiferon TB Gold In-Tube test result (Positive, Negative)	
Tuberculin skin test result (Positive, Negative)	
Has the subject had any Crohn's Disease Related Hospitalizations (Yes, No)	
Has the subject had any Crohn's Disease Related Surgeries (Yes, No)	
Number of open and draining (i.e. not closed) fistulas present	
Locations where open and draining fistulas are present (Perianal, Abdominal, Rectovaginal, Enterovesicular, Other)	
Location of Crohn's Disease (Ileocolonic, Ileal, Colonic, Not applicable)	
Prior exposure to biologics for treatment of Crohn's disease (Biologic naïve, prior exposure to 1 biologic)	

Baseline SES-CD score (SES-CD $\leq 16$ , SES CD $>16$ )		
EQ-5D-5L levels of each of the 5 dimensions i.e. mobility, self-care, usual activities, pain/discomfort and anxiety/depression		
HADS-A and HADS-D subscale scores for anxiety and depression categorized as normal (score of 0 to 7), mild (score of 8 to 10), moderate (score of 11 to 14), and severe (score of 15 to 21).		
WPAI: Currently in paid employment (Yes, No) and 7-point improvement (yes, No) for each domain separately		
Number of draining fistulas		

## 4.2. Medical History

The number and percentage of subjects with any abnormality will be summarized overall and per body system. Specifications of abnormalities ongoing at study entry as well as overall will be summarized per body system.

## 4.3. Disposition Information

The number of subjects in each analysis set will be summarized per treatment arm. In addition, the distribution of subjects in the Full Analysis Set by country will be presented.

The subjects randomized at week 16 will be summarized.

For the Full Analysis set the number of subjects per visit will be summarized. Subjects who discontinued study agent prior to Week 48 along with the reasons for discontinuation and the dose regimen at time of discontinuation, and subjects who terminated study participation prior to Week 48 along with the reasons for termination and the dose regimen at time of study termination, will be summarized per treatment arm.

## 4.4. Treatment Compliance

A listing of subjects who were randomized but were never treated will be provided. The number of subjects in the Treat to Target arm who did not meet the treatment target, but dose was not adjusted accordingly, will be summarized as frequency distribution through Week 48 based on the full analysis set. In addition, the number of subjects in the Treat to Target arm for whom dose was adjusted although treatment target was met, will be summarized as frequency distribution. Subjects in the RoC arm for whom dose was adjusted to 4 weekly regimen will be listed.

## 4.5. Extent of Exposure

Whether ustekinumab was administered (yes or no), how it was administered (Administered at site by site staff, Self-injected by patient at site, Self-injected by patient at home) and the dose that was administered, will be summarized by treatment group for each visit through week 48. For week 0 the dose administered will be summarized by body weight category ( $\leq 55$  kg,  $>55$  kg and  $\leq 85$  kg,  $>85$  kg). For each post-baseline visit the number (%) of subjects with a dose adjustment/dose not administered as well as the reason for dose adjustments/doses not administered will be summarized by treatment group and visit. For each visit at or after week 16 the dose regimen assigned and administered will also be summarized by treatment arm. The total number of injections administered as well as total number of injections administered per 4 weeks of treatment exposure, will be summarized descriptively by

treatment arm through Week 48 for the full analysis set, both overall and per assigned regimen at week 16.

The distribution of the time to first optimization of dosing frequency will be displayed with Kaplan-Meier curves, per arm and per assigned regimen at week 16 within each arm. Subjects with any dose optimization from randomization till week 48 at any time will be considered an 'Event' and their date of dose optimization will be used in the time to event calculation. Subjects who complete the 48 weeks or discontinue prior to week 48 without any dose optimization will be censored and the date of completion or discontinuation will serve as the time of censoring.

#### **4.6. Protocol Deviations**

For all randomized subjects the number (%) of subjects with a major protocol deviation through Week 48 will be summarized per treatment arm by the standard categories (Developed withdrawal criteria but not withdrawn; Entered but did not satisfy criteria; Received a disallowed concomitant treatment; Received wrong treatment or incorrect dose; Other).

A listing of subjects who have a major protocol deviation will be provided.

#### **4.7. Prior and Concomitant Medications**

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose of study agent. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continued after the first dose of study agent.

Summaries of prior and concomitant medications in the Full Analysis set will be presented by ATC term. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least one concomitant medication.

The number (%) of subjects that were prior exposed to 1 biologic or were biologic naïve will be summarized. For subjects prior exposed to 1 biologic the generic of the biologic will be summarized as well as the reason for discontinuation of the prior biologic (Inadequate response, Loss of response, Intolerance, Contraindications, Physicians decision, Non-Medical, Unknown, Other reason).

The number (%) of subjects using corticosteroids at study entry, week 8, randomization visit, week 48 visit and at endpoint will be summarized, including descriptive statistics for the prednisone equivalent dose. For the subjects using corticosteroids at randomization visit the number of subjects that were tapered down before week 48 and the number of subjects that started corticosteroids after tapering down will be summarized descriptively.

### **5. EFFICACY**

The efficacy analyses described in this section will be based on the Full Analysis set, i.e. subjects randomized at Week 16 of this study. Results will be reported per treatment group.

#### **5.1. Analysis Specifications**

In general, descriptive statistics (e.g., mean, median, SD, IQ range, 95% CI, minimum and maximum) will be used to summarize continuous and ordinal variables. Counts, percentages and 95% CIs will be used to summarize categorical variables. Graphical data displays (e.g., line plots) may also be used to summarize the data whenever appropriate.

Analyses suitable for categorical data (e.g., chi-square tests, Cochran-Mantel-Haenszel chi-square tests, or logistic regression, as appropriate) will be used to compare the proportions of subjects achieving selected endpoints (e.g., endoscopic response). Continuous response parameters will be compared using an analysis of variance (ANOVA) or covariance (ANCOVA), unless otherwise specified. If the normality assumption is in question, an ANOVA or ANCOVA on the van der Waerden normal scores will be used.

Time to event endpoints will be compared between each of the ustekinumab treatment groups and the using the stratified log-rank test with prior exposure to biologic and baseline SES-CD score ( $\leq 16$  or  $>16$ ) as the stratification factors, unless otherwise specified. The Kaplan-Meier curve by treatment group will be provided

When stratification factors are used for analysis, the stratification factors will not be as determined by the IWRS but will be based on the actual data collected.

### 5.1.1. Level of Significance

All statistical tests will be interpreted at the 5% significance level (2-tailed), unless otherwise specified.

### 5.1.2. Data Handling Rules

Subjects with missing data, defined as those who terminated the study prior to the designated visit or subjects who have a missing value at the designated visit, will be considered to not have achieved their dichotomous efficacy endpoints. For continuous endpoints, the last available post-baseline value will be carried forward for subjects with missing data. In addition observed case analysis can be added.

## 5.2. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is endoscopic response at Week 48, based on the simple endoscopic score for Crohn's disease (SES-CD).

### 5.2.1. Definition

Endoscopic response at Week 48 is defined as showing (yes or no) a reduction from baseline in SES-CD of  $\geq 50\%$ .

### 5.2.2. Estimand

**Population:** adult subjects with moderate to severely active ileal and/or colonic Crohn's disease who previously have had an inadequate response with, lost response to, have been intolerant to, or have medical contraindications to either conventional therapy, or one previous biologic therapy approved for the treatment of Crohn's disease.

**Endpoint:** the proportion of subjects with endoscopic response at Week 48.

**Intercurrent event:** Premature discontinuation of study treatment

**Population-level summary:** the proportion of subjects with endoscopic response at Week 48 for the T2T group vs RoC group.

### 5.2.3. Analysis Methods

For the primary endpoint, the number and proportion of subjects achieving an endoscopic response (defined as a reduction from baseline in SES-CD of  $\geq 50\%$ ) at Week 48 will be summarized. The endpoints will be compared between the T2T treatment group and the RoC treatment group using 2-

sided Cochran Mantel Haenszel chi-square test, stratified by whether the subject was biologic-naïve at baseline/had prior exposure to 1 biologic for treatment of Crohn's disease, and according to baseline SES-CD score  $\leq 16$  or SES-CD  $> 16$  at a significance level of 0.05.

Randomized subjects who stop treatment before reaching Week 48 due to any reason, or subjects without endoscopic data at Week 48 will be analyzed as non-responders.

### Sensitivity Analyses

To assess the robustness of the primary endpoint analysis, the following two sensitivity analyses will be conducted.

- (1) Randomized subjects who stop treatment before reaching Week 48 due to reasons other than lack/loss of efficacy will be excluded from the analysis.
- (2) Last observation carried forward: subjects who have a missing SES-CD score at week 48 or who stopped treatment before reaching week 48 will have their last SES-CD score carried forward.

### 5.3. Other Efficacy Endpoints

The other efficacy endpoints will not be adjusted for multiplicity, and statements of significance for these endpoints will be based on nominal p-values.

#### 5.3.1. Secondary Efficacy Endpoints at (or through) Week 48

Table 4 presents a list of secondary efficacy endpoints that will be summarized.

**Table 4:** Secondary efficacy endpoints

Categorical Variables:	Summary Type
Endoscopic remission (defined as an SES-CD score $\leq 2$ ) at week 16 <sup>a</sup> , week 48 and endpoint <ul style="list-style-type: none"> <li>– all patients</li> <li>– for biologic-naïve and prior exposed to 1 biologic subjects, separately</li> <li>– by SES-CD score at baseline (<math>\leq 16</math>, <math>&gt; 16</math>)</li> </ul>	Frequency distribution with the number and percentage of subjects in each category.
Corticosteroid-free endoscopic response at week 16 <sup>a</sup> , Week 48 and endpoint (defined as a reduction from baseline in SES-CD score of $\geq 50\%$ and not taking any corticosteroids for at least 30 days prior to week 48 and endpoint, respectively) <ul style="list-style-type: none"> <li>– all patients</li> <li>– for the subjects who were receiving corticosteroids at baseline, separately</li> </ul>	
Endoscopic response (50%) at week 16 <sup>a</sup> and endpoint	
Endoscopic response (25%, 100%) at week 16 <sup>a</sup> , week 48 and	



<p>Endoscopic response (25%, 50%, 100%) at week 16<sup>a</sup>, week 48 and endpoint</p> <ul style="list-style-type: none"> <li>– for biologic-naïve and prior exposed to 1 biologic subjects, separately</li> <li>– by SES-CD score at baseline (<math>\leq 16</math>, <math>&gt; 16</math>)</li> <li>– by disease duration (quartiles)</li> <li>– by disease location</li> </ul>		
<p>Mucosal healing defined as the complete absence of mucosal ulcerations in any ileocolonic segment at week 16<sup>a</sup>, week 48 and endpoint</p>		
<p>Clinical remission (CDAI score of <math>&lt; 150</math> points) at week 8, week 16, week 48 and endpoint</p> <ul style="list-style-type: none"> <li>– all patients</li> <li>– for biologic-naïve and prior exposed to 1 biologic subjects, separately</li> </ul>		
<p>Clinical response (<math>\geq 100</math>-point reduction from the baseline CDAI score, or a CDAI score of <math>&lt; 150</math> points) at week 8, week 16, week 48 and endpoint</p> <ul style="list-style-type: none"> <li>– all patients</li> <li>– for biologic-naïve and prior exposed to 1 biologic subjects, separately</li> </ul>		
<p>Corticosteroid-free clinical remission at Week 48 and endpoint (defined as a CDAI score <math>&lt; 150</math> and not taking any corticosteroids for at least 30 days prior to Week 48)</p> <ul style="list-style-type: none"> <li>– all patients</li> <li>– for the subjects who were receiving corticosteroids at baseline, separately</li> </ul>		
<p>CDAI-70 responders at week 8, week 16, week 48 and endpoint</p> <ul style="list-style-type: none"> <li>– all patients</li> <li>– for biologic-naïve and prior exposed to 1 biologic subjects, separately</li> </ul>		
<p>Fistula response (defined as <math>\geq 50\%</math> reduction from baseline in the number of draining fistulas) at Week 48</p>		
<p>Normalized CRP (<math>\text{CRP} \leq 3 \text{ mg/L}</math>) at week 8, week 16 and any assessment visit through and including week 48, and endpoint*</p> <ul style="list-style-type: none"> <li>– all patients</li> <li>– for biologic-naïve and prior exposed to 1 biologic subjects, separately</li> </ul>		

Complete biomarker response (i.e. both CRP and FC should be normalized) at week 8, week 16 and any assessment visit through and including week 48, and endpoint*** <ul style="list-style-type: none"> <li>– all</li> <li>– for biologic-naïve and prior exposed to 1 biologic subjects, separately</li> </ul>	
Complete biomarker response (i.e. both CRP and FC should be normalized) at week 8, week 16 and any assessment visit through and including week 48, and endpoint*** <ul style="list-style-type: none"> <li>– all</li> <li>– for biologic-naïve and prior exposed to 1 biologic subjects, separately</li> </ul>	
Normalized FC ( $FC \leq 250 \mu\text{g/g}$ ) at week 8, week 16 and any assessment visit through and including week 48, and endpoint ** <ul style="list-style-type: none"> <li>– all patients</li> <li>– for biologic-naïve and prior exposed to 1 biologic subjects, separately</li> </ul>	
CRP change (%) from baseline $< 50\%$ , $\geq 50\%$ at week 8, week 16 and any assessment visit through and including week 48, and endpoint <ul style="list-style-type: none"> <li>– all patients</li> <li>– for biologic-naïve and prior exposed to 1 biologic subjects, separately</li> <li>– for subjects with elevated CRP at baseline (i.e. <math>CRP &gt; 3 \text{ mg/L}</math>)</li> <li>– for subjects with elevated CRP at baseline (i.e. <math>CRP &gt; 3 \text{ mg/L}</math>) and biologic-naïve and prior exposed to 1 biologic subjects, separately</li> </ul>	
FC change (%) from baseline $< 50\%$ , $\geq 50\%$ at week 8, week 16 and any assessment visit through and including week 48, and endpoint <ul style="list-style-type: none"> <li>– all patients</li> <li>– for biologic-naïve and prior exposed to 1 biologic subjects, separately</li> <li>– for subjects with elevated FC at baseline (i.e. <math>FC &gt; 250 \mu\text{g/g}</math>)</li> <li>– for subjects with elevated FC at baseline (i.e. <math>FC &gt; 250 \mu\text{g/g}</math>) and biologic-naïve and prior exposed to 1 biologic subjects, separately</li> </ul>	
a : For T2T arm only * : Subjects with normalized CRP at baseline will be excluded ** : Subjects with normalized FC at baseline will be excluded *** : Subjects with normalized CRP and Normalized FC at baseline will be excluded	
<b>Continuous Variables:</b>	<b>Summary Type</b>
SES-CD score at week 0, <u>week 16<sup>a</sup></u> , week 48 and endpoint	Descriptive statistics (N, mean, standard deviation [SD], median, 95% CI and range [minimum and maximum])
SES-CD changes vs. week 0, at week 16 <sup>a</sup> , week 48 and endpoint	
CDAI score at visits week 0, week 8, week 16, week 48 and endpoint	
CDAI changes vs. week 0 at week 8, week 16, week 48 and endpoint	
CRP value at week 0, week 8, week 16 and any assessment visit through and including week 48, and endpoint	
CRP changes vs. week 0 at week 8, week 16 and any assessment visit through and including week 48, and endpoint	

FC value at week 0, week 8, week 16 and any assessment visit through and including week 48, and endpoint	
FC changes vs week 0 at week 8, week 16 and any assessment visit through and including week 48, and endpoint	
a : T2T arm only	

### 5.3.2. Secondary Efficacy Endpoints - PRO Endpoints

Table 5 presents a list of secondary efficacy endpoints – PROs that will be summarized.

**Table 5:** Secondary efficacy endpoints – PRO endpoints

Continuous Variables:	Summary Type
IBDQ total score and change vs. week 0 at week 16, week 48 and endpoint	Descriptive statistics (N, mean, standard deviation [SD], median, 95% CI and range [minimum and maximum])
IBDQ domain scores and change vs. week 0 at week 16, week 48 and endpoint	
EQ-5D-5L VAS and EQ-5D-5L Index score at week 0, week 16, week 48 and endpoint	
EQ 5D-5L VAS and EQ-5D-5L Index changes vs. week 0, week 16, week 48 and endpoint	
FACIT-F score at visits week 0, week 16, week 48 and endpoint	
FACIT F changes vs week 0 at visits week 16, week 48 and endpoint	
HADS score for both Anxiety and Depression at visits week 0, week 16, week 48 and endpoint	
HADS changes vs week 0 for both Anxiety and Depression at visits week 16, week 48 and endpoint	
Categorical Variables:	Summary Type
IBDQ response ( $\geq 16$ -point improvement in IBDQ score from baseline) at week 16, week 48 and endpoint	Frequency distribution with the number and percentage of subjects in each category.
IBDQ remission (IBDQ score $\geq 170$ ) at week 16, week 48 and endpoint	
EQ-5D-5L: Mobility, Self-care, Usual activity, Pain/Discomfort and anxiety/depression at week 0, week 16, week 48 and endpoint	
HADS-A and HADS-D categories (Normal, Mild, Moderate and Severe) at week 0, week 16, week 48 and endpoint	

### 5.3.3. Healthcare resource utilization endpoints

Table 6 presents a list of Healthcare resource utilization endpoints that will be summarized.

**Table 6:** Healthcare resource utilization endpoints

Continuous Variables:	Summary Type
Time lost from work at week 0, week 16, week 48 and endpoint	Descriptive statistics (N, mean, standard deviation [SD], median, 95% CI and range
Time lost from work changes vs week 0 at week 16, week 48 and endpoint	
WPAI scores for Absenteeism, Presenteeism, Work Productivity Loss and Activity Impairment at week 0, week 16, week 48 and endpoint	

WPAI changes vs week 0 for Absenteeism, Presenteeism, Work Productivity Loss and Activity Impairment at week 16, week 48 and endpoint	[minimum and maximum]
<b>Categorical Variables:</b>	<b>Summary Type</b>
Crohn's disease-related hospitalizations and Crohn's disease-related surgeries	Frequency distribution with the number and percentage of subjects in each category.
WPAI: Currently Employed (Yes/No) at week 0, week 16, week 48 and endpoint	
WPAI: 7-point improvement from baseline for each domain	

### 5.3.3.1. Definition

#### 5.3.3.1.1. Video Ileocolonoscopy

Centrally-read ileocolonoscopy will be used to assess SES-CD at week 0, week 16 (for T2T arm only) and week 48 or early termination. The SES CD is a simple, reproducible, and easy-to-use endoscopic scoring system for Crohn's disease, by which endoscopic parameters (ulcer size, ulcerated and affected surfaces, stenosis) are scored from 0 to 3. Endoscopic response is defined as showing (yes or no) a reduction from baseline in SES-CD score of  $\geq 50\%$ . Endoscopic remission is defined as SES-CD score  $\leq 2$ .

Mucosal healing is defined as the complete absence of mucosal ulcerations in any ileocolonic segment.

#### 5.3.3.1.2. Crohn's Disease Activity Index (CDAI)

CDAI is assessed at week 0, week 8, week 16 and week 48 or early termination and is defined as the Total score of the Crohn's Disease Activity Index based information of different Crohn's disease-related variables (attachment 2). These 8 variables are: extra-intestinal manifestations, abdominal mass, weight, hematocrit, total number of liquid stools, abdominal pain/cramping, use of antidiarrheal drug(s) and/or opiates, and general wellbeing. The last 4 variables are scored over 7 days by the subject on a diary card. Subject is defined as CDAI-70 responder at a visit when the CDAI Total Score at that visit is improved with at least 70 points versus baseline.

Clinical response is defined as  $\geq 100$ -point reduction from the baseline CDAI Total score, or a CDAI Total score  $< 150$ .

Clinical remission is defined as CDAI Total score of  $< 150$  points.

#### 5.3.3.1.3. C-reactive Protein and Fecal Calprotectin

C-reactive protein and fecal calprotectin will be evaluated at week 0, week 8, week 16, each assessment or disease flare visit during maintenance, and week 48 or early termination, to monitor efficacy.

Normalized CRP is defined as  $\text{CRP} \leq 3 \text{ mg/L}$  and normalized FC is defined as  $\text{FC} \leq 250 \text{ } \mu\text{g/g}$ . Complete biomarker response is defined as both CRP and FC normalized. Subjects with normalized CRP and Normalized FC at baseline will be excluded for the analysis of complete biomarker response.

#### 5.3.3.1.4. Fistula Assessment

All subjects will be assessed for fistulas at week 0 and week 48 or early termination. For subjects with fistulizing disease, fistula closure will be assessed. For subjects with fistulas at baseline fistula response at week 48 will be analyzed, defined as  $\geq 50\%$  reduction from baseline in the number of draining fistulas.

### 5.3.3.1.5. Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ, assessed at week 0, week 16 and week 48 or early termination, is a 32-item self-report questionnaire (attachment 3) for subjects with IBD to evaluate the PROs across 4 dimensions: bowel symptoms (loose stools, abdominal pain), systemic symptoms (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional function (anger, depression, irritability). IBDQ Total score will be defined as the total of the 32 IBDQ questions and will range from 32 to 224 with higher score indicating better quality of life. IBDQ domain scores are based on the following 4 dimensions:

- Bowel symptoms (question 1, 5, 9, 13, 17, 20, 22, 24, 26, 29)
- Emotional function (questions 3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32)
- Systemic symptoms (question 2, 6, 10, 14, 18)
- Social Function (questions 4, 8, 12, 16, 28)

IBDQ response is defined as achieving a  $\geq 16$ -point improvement in IBDQ score from baseline.

IBDQ remission is defined as achieving a IBDQ score  $\geq 170$ .

### 5.3.3.1.6. EuroQoL-5D-5L Health Questionnaire (EQ-5D-5L)

The EQ-5D-5L (attachment 4) is a frequently used generic instrument to measure health-related QoL assessed at week 0, week 16 and week 48 or early termination. It comprises 5 dimensions, i.e. mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems and 5=extreme problems.

The EQ-5D-5L VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints 100 labelled 'the best health you can imagine' and 0 labelled 'the worst health you can imagine'.

With the levels of the 5 dimensions the EQ-5D-5L index value is calculated describing the respondent's health state ranging from 0 to 1, with higher index value indicating better health state.

### 5.3.3.1.7. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

The FACIT-F scale, assessed at week 0, week 16 and week 48 or early termination, is a 13-item fatigue scale with a 7-day recall period (attachment 5). It measures the level of fatigue during the usual daily activities. The level of fatigue is measured on a 4-point Likert scale (0=very much fatigued to 4=not at all fatigued). The higher the score the better the QoL.

### 5.3.3.1.8. Hospital Anxiety and Depression Scale (HADS)

The HADS (attachment 6) is a validated 14-item scale with 7 of the items relating to anxiety and 7 relating to depression, assessed at week 0, week 16 and week 48 or early termination. Each item is scored from 0 to 3, with higher scores indicating greater likelihood of depression or anxiety. Cases of anxiety or depression are each defined by subscale scores of 8 or greater and categorized as normal (score of 0 to 7), mild (score of 8 to 10), moderate (score of 11 to 14), and severe (score of 15 to 21).

### 5.3.3.1.9. Work Productivity and Activity Impairment (WPAI)

The WPAI, assessed at week 0, week 16 and week 48 or early termination, is a validated 6-question instrument that measures the effect of CD symptoms on a subject's ability to work and perform normal daily activities (attachment 7). The recall period for the WPAI-CD is up to the previous 7 days.

### 5.3.3.1.10. Time Lost From Work

Time lost from work will be collected at week 0, week 16 and week 40 or early termination, by asking the subjects a single question, “How many days did you miss from work due to your Crohn’s disease in the last 4 weeks?”

### 5.3.3.2. Analysis Methods

Descriptive statistics will include counts and percentages for categorical data, and median, mean, SD, 95% CI, and range for continuous data.

The proportions will be summarized and compared between the two treatment groups using 2-sided Cochran-Mantel Haenszel-chi-square test, stratified by whether the subject was biologic naïve at baseline/had prior exposure to 1 biologic for treatment of Crohn’s disease, and by baseline SES-CD score ( $\leq 16$  or  $>16$ ), unless otherwise specified.

Continuous response parameters (such as changes from baseline) will be compared between the treatment groups using an analysis of covariance (ANCOVA), with baseline value and stratification factors as a covariate, unless otherwise specified. If the normality assumption is in question, an ANCOVA on the van der Waerden normal scores will be used. Nominal p values will be presented for all analyses unless specified otherwise.

### 5.3.3.3. Data Handling Rules

#### 5.3.3.3.1. Video- Ileocolonoscopy

If SES-CD is missing at week 0 or week 48 subject will be categorized as ‘Non-responder’.

#### 5.3.3.3.2. CDAI

Subjects with a missing CDAI Total score at week 48 will be labeled ‘Non-responder’ for CDAI-70 response at week 48. Same approach is used for CDAI-70 responder as well as for Clinical remission and Clinical response at each visit analyzed.

#### 5.3.3.3.3. IBDQ

Total IBDQ score will be the sum of the scores of the 32 items if no more than 4 questions are missing for the full IBDQ. If no response is given for a particular question, provided only one response per domain is missing, the score should be imputed by the mean score of the other items in the domain. If more than 4 questions are missing, then total IBDQ score will be left missing. If more than 1 item is missing in a domain, the score for that domain will be left missing.

Calculation for the 4 domains will be as follows:

**Bowel symptoms:** Add up scores for questions (1, 5, 9, 13, 17, 20, 22, 24, 26, 29).

**Emotional function:** Add up scores for questions (3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32).

**Systemic symptoms:** Add up scores for questions (2, 6, 10, 14, 18).

**Social function:** Add up scores for questions (4, 8, 12, 16, 28).

**5.3.3.3.4. EQ-5D-5L**

The EQ-5D descriptive system can be converted into a single summary EQ-5D Index. EQ-5D index scores in this analysis will be derived with the algorithm and software provided by the developer based on the UK model.

**5.3.3.3.5. HADS**

The sum of the 7 items relating to Anxiety provides the Total score for Anxiety and the sum of the 7 items relating to Depression provides the Total score for Depression (attachment 6).

**5.3.3.3.6. FACIT-F**

The Fatigue Subscale score is the sum of the 13-item score. First reversals for all items scores (except Question 7 (I have energy) and Question 8 (I am able to do my usual activities)) should be performed. The sum of these reversed item scores should be multiplied by 13 and divided by the number items answered (attachment 5). Missing items in each subscale will be imputed with the subscale mean value unless more than half of the items are missing.

**5.3.3.3.7. WPAI**

The WPAI:CD is a validated, self-administered questionnaire that assesses work and activity impairment during the past 7 days (see attachment 7). The WPAI produces 4 types of scores:

- Absenteeism (work time missed)
- Presenteeism (impairment at work/reduced on-the-job effectiveness)
- Work Productivity Loss (overall work impairment/absenteeism plus presenteeism)
- Activity Impairment.

The WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes.

***Scoring system***

Questions:

Q1 = currently employed

Q2 = hours missed due to Crohn's Disease

Q3 = hours missed other reasons

Q4 = hours actually worked

Q5 = degree Crohn's Disease affected productivity while working

Q6 = degree Crohn's Disease affected regular activities

Multiply scores by 100 to express in percentages.

- Percent work time missed (absenteeism) due to Crohn's Disease:  $100 * Q2/(Q2+Q4)$
- Percent impairment while working (presenteeism) due to Crohn's Disease:  $100 * Q5/10$
- Percent overall work impairment (work productivity loss) due to Crohn's Disease:

$$100\% * \left[ \frac{Q2}{Q2 + Q4} + \left( \left( 1 - \left( \frac{Q2}{Q2 + Q4} \right) \right) * \left( \frac{Q5}{10} \right) \right) \right]$$

- Percent activity impairment due to Crohn's Disease:  $100 * Q6/10$

For the WPAI the following will be provided:

For all visits through week 48 and LOCF endpoint, the number (%) of patients who are 'Currently Employed' will be summarized.

The 4 WPAI parameters are analyzed separately. The Activity Impairment score is calculated for all patients. The Absenteeism, Presenteeism and Work Productivity Loss scores are calculated only for currently employed patients (variable Currently Employed=YES).

#### 5.3.3.4. Treatment failure rules

No treatment failure rules are applied.

#### 5.3.3.5. Missing Data Imputation

Subjects with missing data, defined as those who terminated the study prior to the designated visit or subjects who have a missing value at the designated visit, will be considered to not have achieved their dichotomous efficacy endpoints. For continuous endpoints, the last available value will be carried forward for subjects with missing data. Observed data for continuous endpoint will also be available.

### 6. Exploratory IUS Variable(s)

Intestinal ultrasound (IUS) assessments have been performed on a subgroup of the total population (substudy of CNT01275CRD3005). Participation in this substudy was optional for subjects participating in the main study. IUS assessments are performed at week 0, week 4, week 8, week 16 and week 48. The gastroenterologist or radiologist performing ultrasonography at the study site will be neither the person performing ileocolonoscopy, nor the investigator making prescribing decisions.

Table 8 presents a list of IUS variables that will be summarized for the IUS Analysis set. Results will be reported per treatment arm and overall, unless otherwise specified. The analysis on IUS variables will be as observed. As a sensitivity analysis NRI imputation for response variables and LOCF for continuous variables might be done.

**Table 8:** IUS Variables descriptive statistics

Categorical Variables:	Summary Type
Summary of the most affected part of the bowel at week 0	Frequency distribution with the number and percentage of subjects in each category.
IUS response at week 4, 8, 16 and week 48 for the most affected part of the bowel as well as for most affected part of the bowel being Ileum or Colon	
IUS remission at week 4, 8, 16 and week 48 for the most affected part of the bowel as well as for most affected part of the bowel being Ileum or Colon	
Percentage of subjects with normalization of BWT at week 0, 4, 8, 16 and week 48 for the most affected part of the bowel as well as for most affected part of the bowel being Ileum or Colon	
Percentage of subjects with normalization of color Doppler signal (defined as $\leq 1$ ) at week 0, 4, 8, 16 and week 48 for the most affected part of the bowel as well as for most affected part of the bowel being Ileum or Colon	



Percentage of subjects with normalization of echostratification (defined as normal/preserved echostratification) at week 0, 4, 8, 16 and week 48 for the most affected part of the bowel as well as for most affected part of the bowel being Ileum or Colon	
Percentage of subjects with normalization of inflammatory mesenteric fat at week 0, 4, 8, 16 and week 48 for the most affected part of the bowel as well as for most affected part of the bowel being Ileum or Colon	
Fasting status at week 0, 4, 8, 16 and week 48	
<b>Continuous variables:</b>	Descriptive statistics (N, mean, standard deviation [SD], median, 95% CI and range [minimum and maximum])
BWT at baseline, week 4, week 8, 16 and week 48 and change (both absolute and %) from baseline in BWT in mm at week 4, 8, 16 and week 48 for the most affected part of the bowel, as well as for most affected part of the bowel being Ileum or Colon	

Table 9 presents a list of IUS variables that will be cross-tabulated or correlated with clinical variables for the IUS Analysis set. Results will be reported on the overall analysis set, not per treatment arm.

**Table 9:** Correlation of IUS Variables and clinical data

Correlations	Summary
Normalization of BWT (Yes, No) of the most affected segment versus SES-CD ( $\leq 16$ , $> 16$ ) at baseline and week 48	Number and percentage within each class and Cohen's Kappa statistic for agreement at each visit.
Normalization of Pathologic BWT of the most affected segment (Yes, No) versus <ul style="list-style-type: none"> <li>• CDAI (score <math>&lt; 220</math>, <math>\geq 220</math>)</li> <li>• CRP (<math>\leq 10</math> mg/L, <math>&gt; 10</math> mg/L)</li> <li>• CRP (<math>\leq 3</math> mg/L, <math>&gt; 3</math> mg/L)</li> <li>• FC (<math>\leq 250</math> <math>\mu</math>g/g, <math>&gt; 250</math> <math>\mu</math>g/g)</li> </ul> at baseline, week 8, week 16 and week 48	

<p>Correlation of IUS response at week 4, week 8 and week 16 vs. clinical outcome and biomarkers at week 8, week 16 and week 48:</p> <ul style="list-style-type: none"> <li>• Clinical outcome <ul style="list-style-type: none"> <li>○ CDAI-70 responders</li> <li>○ Clinical remission</li> <li>○ Clinical response</li> <li>○ SES-CD improvement at week 48 vs. week 0 <ul style="list-style-type: none"> <li>▪ &lt; 25%, ≥ 25%</li> <li>▪ &lt; 50%, ≥ 50%</li> <li>▪ &lt; 100%, 100%</li> </ul> </li> </ul> </li> <li>• Biomarkers <ul style="list-style-type: none"> <li>○ Normalized CRP (CRP ≤ 3 mg/L)</li> <li>○ Normalized FC (FC ≤ 250 µg/g)</li> <li>○ Complete biomarker response</li> <li>○ CRP change (%) from baseline &lt; 50%, ≥ 50%</li> <li>○ FC change (%) from baseline &lt; 50%, ≥ 50%</li> </ul> </li> </ul>	
<p>Correlation of BWT value and change from baseline of the most affected segment versus</p> <ul style="list-style-type: none"> <li>• SES-CD value</li> </ul> <p>At baseline and Week 48</p>	<p>Descriptive statistics and Spearman correlation coefficient for both the values at each visit and the changes from baseline</p>
<p>Correlation of BWT value and change from baseline of the most affected segment versus</p> <ul style="list-style-type: none"> <li>• CDAI value</li> <li>• CRP value</li> <li>• FC value</li> </ul> <p>At baseline, Week 8, Week 16 and Week 48</p>	
<p>Correlation of Color Doppler, Echostratification, and Inflammatory Mesenteric Fat of the most affected part of the bowel with</p> <ul style="list-style-type: none"> <li>• FC (all subjects and those with abnormal FC at baseline)</li> <li>• CDAI</li> <li>• SES-CD</li> </ul> <p>At baseline, Week 8, Week 16 and Week 48 for FC and CDAI and at baseline and Week 48 for SES-CD</p>	

## 6.1. Definition

Bowel wall thickness will be determined as the mean of 4 measurements (2 in transverse and 2 in longitudinal section) of the most affected part of each bowel segment (ie, terminal ileum, cecum, ascending colon, transverse colon, and sigmoid colon).

IUS response is defined as showing (yes or no) a reduction from week 0 in BWT of  $\geq 25\%$ .

IUS remission defined as normalization of all the 4 IUS parameters:

- BWT
- Vascularization (color Doppler signal)
- Echostratification
- Inflammatory mesenteric fat.

Normalization of the IUS parameters is defined as:

- BWT; normalization of BWT will be defined as  $\leq 2.0$  mm for the terminal ileum and  $\leq 3.0$  mm for the colon (i.e. cecum, ascending colon, transverse colon, and sigmoid colon);
- Vascularization (color Doppler signal); normalization of color Doppler signal will be defined as  $\leq 1$ ;
- Echostratification; normalization of echostratification will be defined as normal/preserved echostratification;
- Inflammatory mesenteric fat; normalization of inflammatory mesenteric fat will be defined as absence of inflammatory fat.

Bowel wall thickness will be assessed at each substudy visit. Other IUS parameters will only be determined if BWT is pathologic (ie,  $> 2.0$  mm for the terminal ileum;  $> 3.0$  mm for the colon), in which case the same parts of the bowel segments that are used for measurement of BWT will also be assessed for vascularization (color Doppler signal), echostratification, and inflammatory mesenteric fat. Analyses of IUS response and IUS remission will be based on the most affected (most thickened) part of the bowel wall.

### 6.1.1. Analysis Methods

For the analysis of IUS response and IUS remission the most affected part of the bowel at week 0 should be determined, based on the BWT for each of the 5 segments. IUS response and IUS remission will be calculated based on this most affected segment.

Descriptive statistics of each IUS endpoint will be used to summarize the data per treatment arm and overall. To explore the correlation between continuous IUS and clinical endpoints, Spearman correlation coefficient will be reported, and the total population will be used. Overall population will also be used to analyze the agreement between categorical IUS and clinical endpoints and Cohen's Kappa statistic will be reported. Kappa results will be interpreted, as suggested by Cohen:

values  $\leq 0$  as indicating no agreement  
 0.01–0.20 as none to slight  
 0.21–0.40 as fair  
 0.41–0.60 as moderate  
 0.61–0.80 as substantial  
 0.81–1.00 as almost perfect agreement

For calculating the level of agreement, Pathologic BWT will be considered as the new test and the 4 clinical variables SES-CD, CDAI, CRP and FC as the imperfect reference test.

		Imperfect Reference test:	
		Level 1	Level 2
New Test: Pathologic BWT	No	a	b
	Yes	c	d
Total		a + c	b + d

Level 1 and level 2 depends on the clinical variable (see table below).

Clinical variable	Level 1	Level 2
SES-CD	$\leq 16$	$> 16$
CDAI	$< 220$	$\geq 220$
CRP	$\leq 10$ mg/L	$> 10$ mg/L
CRP	$\leq 3$ mg/L	$> 3$ mg/L
FC	$\leq 250$ $\mu$ g/g	$> 250$ $\mu$ g/g

Same approach will be used for the correlation of IUS response versus clinical data and biomarker data using the following levels 1 and 2.

Variable	Level 1	Level 2
IUS response	Yes	No
CDAI-70 response	$\leq 16$	$> 16$
Clinical response	$< 220$	$\geq 220$
Clinical remission	$\leq 10$ mg/L	$> 10$ mg/L
SES-CD improvement of		
25%	$\geq 25\%$	$< 25\%$
50%	$\geq 50\%$	$< 50\%$
100%	100%	$< 100\%$
CRP	$\leq 3$ mg/L	$> 3$ mg/L
FC	$\leq 250$ $\mu$ g/g	$> 250$ $\mu$ g/g
Complete biomarker response	Yes	No
CRP change (%) from baseline	$\geq 50\%$	$< 50\%$
FC change (%) from baseline	$\geq 50\%$	$< 50\%$

## 7. SAFETY

All safety analyses will be based on the safety analysis set, unless otherwise specified.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

## 7.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study agent through the day of last dose administered during the maintenance phase plus 16 weeks (unless event started in extension phase), is considered to be treatment emergent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group and overall.

Summary tables will be provided for treatment-emergent adverse events:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study agent/termination of study participation
- AEs by severity
- AEs by relationship to study agent

In addition to the summary tables, listings will be provided for subjects who:

- Had SAEs
- Had AEs leading to discontinuation of study agent/termination of study participation

Incidence of the following treatment-emergent adverse events of special interest will be summarized.

- infusion reactions
- injection-site reactions
- infections, including infections requiring oral or parenteral antimicrobial treatment
- serious infections.

Inclusion of any AE into the class of Infusion reactions, Injection-site reactions or Infections is based on the checkboxes on the AE CRF page and are based on investigator judgment.

A listing of subjects who died during the maintenance phase will be provided.

## 7.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including weight, pulse, blood pressure (systolic and diastolic), and Body Mass Index (BMI) will be summarized at each assessment time point during induction and maintenance phase. Body Mass Index will be calculated as  $\text{weight (kg)} / (\text{height (m)})^2$ , at each time point that body weight is measured. The height measurement collected at screening/week 0 will be used in the calculation. Changes from baseline will be summarized by visits up till week 48. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented by visit and treatment group.

## **8. PHARMACOKINETICS/PHARMACODYNAMICS**

PK analyses will be based on the PK Analysis Set.

### **8.1. Pharmacokinetics**

Blood samples for determining the serum ustekinumab concentrations will be drawn at Weeks 0 (both preadministration and 1 hour postadministration), 8, 16, each assessment visit during maintenance phase and at week 48 or if applicable at early termination, according to the Time and Events Schedule in the protocol.

Serum ustekinumab concentrations will be summarized through Week 48 for the PK Analysis Set. All serum ustekinumab concentration summaries will be based on observed data (i.e., no data imputation). Concentrations below the lowest quantifiable concentration will be treated as 0 in the summary statistics and labeled as 0 in any listings that contain serum concentration data. The proportion of subjects with concentration below the lowest quantifiable concentrations at each visit will be summarized by treatment group. All serum ustekinumab concentration summaries for a particular visit will include data obtained from treated subjects at the visit of interest without imputing any missing data.

In addition, serum ustekinumab concentrations will be summarized through Week 48 by Biologic-naïve and prior exposure to biologic subjects at baseline.

An evaluation of ustekinumab concentration (quartiles) versus the change from baseline in CDAI total score at Week 8, week 16 and week 48, the change from baseline in SES-CD score at week 48, the change from baseline in CRP at week 8, week 16 and week 48 as well as the change from baseline in FC score at week 8, week 16 and week 48 will also be performed to determine the influence of ustekinumab concentration on the efficacy of ustekinumab induction therapy.

An evaluation of ustekinumab concentration versus CDAI-70 responder, Clinical remission, Clinical Response, Normalization of CRP and Normalization of FC at week 8, week 16 and week 48 will be performed as well as the evaluation of ustekinumab concentration versus Endoscopic response (both 25% and 50% improvement) as well as endoscopic remission at week 48 to determine the influence of ustekinumab concentration on the efficacy of ustekinumab induction therapy.

As an exploratory analysis ustekinumab concentrations versus IUS response and IUS remission at week 8, week 16 and week 48 will be performed.

Descriptive statistics (N, mean, SD, median, range) will be used to summarize Ustekinumab concentrations at each sampling time point.

In particular, the following efficacy endpoints will be summarized by ustekinumab concentrations (<1st quartile, >= 1st quartile and < 2nd quartile, >= 2nd quartile and < 3rd quartile, and >= 3rd quartile):

1. Ustekinumab concentrations (quartiles) at week 8 vs
  - a. CDAI change at week 8
  - b. CRP change at week 8
  - c. FC change at week 8
2. Ustekinumab concentrations (quartiles) at week 16 vs
  - a. CDAI change at week 16
  - b. CRP change at week 16
  - c. FC change at week 16
3. Ustekinumab concentrations (quartiles) at week 48 vs
  - a. CDAI change at week 48
  - b. SES-CD change at week 48
  - c. CRP change at week 48
  - d. FC change at week 48
4. Ustekinumab concentrations (quartiles) at week 8 vs
  - a. CDAI-70 responder at Week 8
  - b. Clinical remission at Week 8
  - c. Clinical response at week 8
  - d. IUS response at week 8
  - e. IUS remission at week 8
5. Ustekinumab concentrations (quartiles) at week 16 vs
  - a. CDAI-70 responder at Week 16
  - b. Clinical remission at Week 16
  - c. Clinical response at week 16
  - d. Endoscopic response (25% improvement) at week 16
  - e. Endoscopic response (50% improvement) at week 16
  - f. Endoscopic remission at week 16
  - g. IUS response at week 16
  - h. IUS remission at week 16
6. Ustekinumab concentrations (quartiles) at week 48 vs
  - a. CDAI-70 responder at Week 48
  - b. Clinical remission at Week 48
  - c. Clinical response at week 48
  - d. Endoscopic response (25% improvement) at week 48
  - e. Endoscopic response (50% improvement) at week 48
  - f. Endoscopic remission at week 48
  - g. IUS response at week 48
  - h. IUS remission at week 48

## 8.2. Immunogenicity

Blood samples will be collected to determine immunogenicity to ustekinumab at Weeks 0, 8, 16, each assessment visit during maintenance phase and week 48, and if applicable, at early termination visit according to the Time and Events Schedule in the protocol. The incidence and titers of antibodies to ustekinumab through 16 weeks will be summarized for all subjects in the PK Analysis Set who have appropriate samples for detection of antibodies to ustekinumab (ie, subjects with at least 1 sample obtained after their dose of ustekinumab).

In addition, the Neutralizing Antibody (NAB) Status will be summarized through week 48 for the PK Analysis Set.

An evaluation of antibody to ustekinumab status versus Endoscopic response, Clinical response, CDAI-70 response and clinical remission at week 48 will be performed based on the PK Analysis Set to determine the influence of antibodies to ustekinumab on the efficacy of ustekinumab, if the number of subjects with positive antibody status permits.

A listing of subjects who are positive for antibodies to ustekinumab through week 48 visit will be provided.

## **9. HEALTH ECONOMICS**

Health Economics parameter are described in section 5.3.4. Healthcare resource utilization endpoints.

## **REFERENCES**

## **ATTACHMENTS**

### **1. STATISTICAL ANALYSIS PLAN FOR INTERIM ANALYSIS**



CNTO1275CRD3005  
-IAWK16-SAP final v:



**2. CROHN'S DISEASE ACTIVITY INDEX (SAMPLE)**

DISEASE ACTIVITY INDEX	SUM	X FACTOR	=	SUBTOTAL
Total number of liquid or very soft stools in the previous 7 days	_____	x 2	=	_____
Sum abdominal pain/cramps ratings (total for previous 7 days):	_____	x 5	=	_____
0 = none      2 = moderate 1 = mild      3 = severe				
General <u>well being</u> (total for previous 7 days):	_____	x 7	=	_____
0 = generally well      3 = very poor 1 = slightly under par      4 = terrible 2 = poor				
Categories currently present and <u>presumed to be related to Crohn's disease</u> : 0 = no; 1 = yes				
<input type="checkbox"/> = arthritis/arthralgia	_____	x 20	=	_____
<input type="checkbox"/> = iritis/uveitis	_____	x 20	=	_____
<input type="checkbox"/> = erythema nodosum/pyoderma gangrenosum/aphthous stomatitis	_____	x 20	=	_____
<input type="checkbox"/> = anal fissure, fistula or abscess	_____	x 20	=	_____
<input type="checkbox"/> = <u>other</u> fistula	_____	x 20	=	_____
<input type="checkbox"/> = fever over 100° F (37.8° C) during the previous 7 days.	_____	x 20	=	_____
During the previous 7 days has <u>subject</u> received antidiarrheal therapy at least once:				
<b>OR</b>	_____	x 30	=	_____
During the previous 7 days has subject received opiate therapy on each of the 7 days:				
0 = no 1 = yes				
Abdominal mass:	_____	x 10	=	_____
0 = none    2 = questionable    5 = definite				
Hematocrit:	_____	x 6	=	_____
Males: (47-Hct) = SUM		(add or subtract by sign)		
Females: (42-Hct) = SUM				
*				
$\frac{(\text{Standard Weight} - \text{Actual Body Weight})}{\text{Standard Weight}} \times 100 =$	_____	x 1	=	_____
		(add or subtract by sign, round to 3 decimal places)		

\* If this value is less than -10 then enter -10 here.

Standard weight and actual weight must be in same units (kg or ~~lb~~)

TOTAL = \_\_\_\_\_  
(round total to integer)

### 3. INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

#### For Regulatory Submissions Only

#### INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire, the IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has a graded response numbered from 1 through 7. Please read each question carefully and answer the number which best describes how you have been feeling in the past 2 weeks.

#### EXAMPLE

**How often have you felt unwell as a result of your bowel problem in the past 2 weeks?**

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the nurse questions after completing the questionnaire. This takes only a few minutes to complete.

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QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

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This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from
  - 1 BOWEL MOVEMENTS THE MOST FREQUENT YOU HAVE EVER EXPERIENCED
  - 2 EXTREMELY FREQUENT
  - 3 VERY FREQUENT
  - 4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
  - 5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
  - 6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
  - 7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
  
2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from
  - 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
  
3. How often during the last 2 weeks have you felt frustrated, impatient or restless? Please choose an option from
  - 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
  
4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from
  - 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME

- 
5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from
- 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
6. How much energy have you had during the last 2 weeks? Please choose an option from
- 1 NO ENERGY AT ALL
  - 2 VERY LITTLE ENERGY
  - 3 A LITTLE ENERGY
  - 4 SOME ENERGY
  - 5 A MODERATE AMOUNT OF ENERGY
  - 6 A LOT OF ENERGY
  - 7 FULL OF ENERGY
7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from
- 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from
- 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from
- 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
-

- 
10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from
- 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
11. How often during the last 2 weeks have you been troubled because of fear of not finding a toilet? Please choose an option from
- 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from
- 1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
  - 2 A LOT OF DIFFICULTY
  - 3 A FAIR BIT OF DIFFICULTY
  - 4 SOME DIFFICULTY
  - 5 A LITTLE DIFFICULTY
  - 6 HARDLY ANY DIFFICULTY
  - 7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES
13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from
- 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
14. How often during the last 2 weeks have you had problems getting a good night's sleep or been troubled by waking up during the night? Please choose an option from
- 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
-

- 
- 4 SOME OF THE TIME  
5 A LITTLE OF THE TIME  
6 HARDLY ANY OF THE TIME  
7 NONE OF THE TIME
15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from
- 1 ALL OF THE TIME  
2 MOST OF THE TIME  
3 A GOOD BIT OF THE TIME  
4 SOME OF THE TIME  
5 A LITTLE OF THE TIME  
6 HARDLY ANY OF THE TIME  
7 NONE OF THE TIME
16. How often during the last 2 weeks have you had to avoid attending events where there was no toilet close at hand? Please choose an option from
- 1 ALL OF THE TIME  
2 MOST OF THE TIME  
3 A GOOD BIT OF THE TIME  
4 SOME OF THE TIME  
5 A LITTLE OF THE TIME  
6 HARDLY ANY OF THE TIME  
7 NONE OF THE TIME
17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of wind? Please choose an option from
- 1 A MAJOR PROBLEM  
2 A BIG PROBLEM  
3 A SIGNIFICANT PROBLEM  
4 SOME TROUBLE  
5 A LITTLE TROUBLE  
6 HARDLY ANY TROUBLE  
7 NO TROUBLE
18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be at? Please choose an option from
- 1 A MAJOR PROBLEM  
2 A BIG PROBLEM  
3 A SIGNIFICANT PROBLEM  
4 SOME TROUBLE  
5 A LITTLE TROUBLE  
6 HARDLY ANY TROUBLE  
7 NO TROUBLE
19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from
-

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

- 1 NONE OF THE TIME
- 2 A LITTLE OF THE TIME
- 3 SOME OF THE TIME
- 4 A GOOD BIT OF THE TIME
- 5 MOST OF THE TIME
- 6 ALMOST ALL OF THE TIME
- 7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the toilet even though your bowels were empty? Please choose an option from
- 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from
- 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from
- 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from
- 1 ALL OF THE TIME
  - 2 MOST OF THE TIME
  - 3 A GOOD BIT OF THE TIME
  - 4 SOME OF THE TIME
  - 5 A LITTLE OF THE TIME
  - 6 HARDLY ANY OF THE TIME
  - 7 NONE OF THE TIME
28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from
- 1 NO SEX AS A RESULT OF BOWEL DISEASE
  - 2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
  - 3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
  - 4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
  - 5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
  - 6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE



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7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or an upset stomach? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

- 1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
- 2 GENERALLY DISSATISFIED, UNHAPPY
- 3 SOMEWHAT DISSATISFIED, UNHAPPY
- 4 GENERALLY SATISFIED, PLEASED
- 5 SATISFIED MOST OF THE TIME, HAPPY
- 6 VERY SATISFIED MOST OF THE TIME, HAPPY
- 7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

**4. EUROQOL-5D-5L HEALTH QUESTIONNAIRE (EQ-5D-5L) – SAMPLE UK ENGLISH VERSION**



**Health Questionnaire**

**English version for the UK**

*UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group*

Under each heading, please tick the ONE box that best describes your health TODAY.

### MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

### SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

### USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

### PAIN / DISCOMFORT

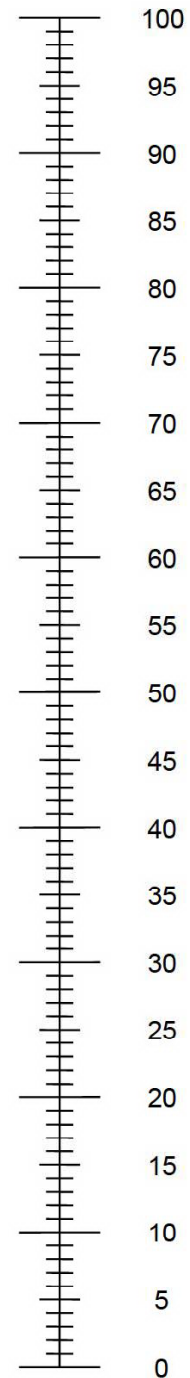
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

### ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.  
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health  
you can imagineThe worst health  
you can imagine

## 5. FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY-FATIGUE (FACIT-F)

### Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not At All	A Little Bit	Somewhat	Quite a Bit	Very Much
1	I feel fatigued	0	1	2	3	4
2	I feel weak all over	0	1	2	3	4
3	I feel listless ("washed out")	0	1	2	3	4
4	I feel tired	0	1	2	3	4
5	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
6	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
7	I have energy	0	1	2	3	4
8	I am able to do my usual activities	0	1	2	3	4
9	I need to sleep during the day	0	1	2	3	4
10	I am too tired to eat	0	1	2	3	4
11	I need help doing my usual activities	0	1	2	3	4
12	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13	I have to limit my social activity because I am tired	0	1	2	3	4

Scoring: Items are scored as follows: 4=Not At All; 3=A Little Bit; 2=Somewhat; 1=Quite A Bit; 0=Very Much, EXCEPT items #7 and #8 which are reversed scored. Score range 0-52. A score of less than 30 indicates severe fatigue. The higher the score, the better the quality of life.

Item Number	Reverse Item?		Item Response	Item Score
1	4	-		=
2	4	-		=
3	4	-		=
4	4	-		=
5	4	-		=
6	4	-		=
7	0	+		=
8	0	+		=
9	4	-		=
10	4	-		=
11	4	-		=
12	4	-		=
13	4	-		=

Sum individual item scores: \_\_\_\_\_

Multiply by 18: \_\_\_\_\_

Divide by number of items answered: \_\_\_\_\_

Source: <http://www.facit.org/FACITOrg/Questionnaires>

**6. HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS) [SAMPLE]****Hospital Anxiety and Depression Scale (HADS)**

**Instructions:** Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

<b>I feel tense or 'wound up':</b>	<b>A</b>	<b>I feel as if I am slowed down:</b>	<b>D</b>
Most of the time	3	Nearly all of the time	3
A lot of the time	2	Very often	2
Time to time, occasionally	1	Sometimes	1
Not at all	0	Not at all	0
<b>I still enjoy the things I used to enjoy:</b>	<b>D</b>	<b>I get a sort of frightened feeling like 'butterflies in the stomach':</b>	<b>A</b>
Definitely as much	0	Not at all	0
Not quite so much	1	Occasionally	1
Only a little	2	Quite often	2
Not at all	3	Very often	3
<b>I get a sort of frightened feeling like something awful is about to happen:</b>	<b>A</b>	<b>I have lost interest in my appearance:</b>	<b>D</b>
Very definitely and quite badly	3	Definitely	3
Yes, but not too badly	2	I don't take as much care as I should	2
A little, but it doesn't worry me	1	I may not take quite as much care	1
Not at all	0	I take just as much care as ever	0
<b>I can laugh and see the funny side of things:</b>	<b>D</b>	<b>I feel restless as if I have to be on the move:</b>	<b>A</b>
As much as I always could	0	Very much indeed	3
Not quite so much now	1	Quite a lot	2
Definitely not so much now	2	Not very much	1
Not at all	3	Not at all	0
<b>Worrying thoughts go through my mind:</b>	<b>A</b>	<b>I look forward with enjoyment to things:</b>	<b>D</b>
A great deal of the time	3	A much as I ever did	0
A lot of the time	2	Rather less than I used to	1
From time to time but not too often	1	Definitely less than I used to	3
Only occasionally	0	Hardly at all	2
<b>I feel cheerful:</b>	<b>D</b>	<b>I get sudden feelings of panic:</b>	<b>A</b>
Not at all	3	Very often indeed	3
Not often	2	Quite often	2
Sometimes	1	Not very often	1
Most of the time	0	Not at all	0
<b>I can sit at ease and feel relaxed:</b>	<b>A</b>	<b>I can enjoy a good book or radio or TV programme:</b>	<b>D</b>
Definitely	0	Often	0
Usually	1	Sometimes	1
Not often	2	Not often	2
Not at all	3	Very seldom	3

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Questions relating to anxiety are indicated by an 'A' while those relating to depression are shown by a 'D'. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over indicating clinical 'caseness'.

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**7. WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT (WPAI) [SAMPLE]**

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The following questions ask about the effect of your Crohn's disease on your ability to work and perform normal daily activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently in paid employment? \_\_\_\_\_ NO \_\_\_\_\_ YES  
*NO, tick "NO" and skip to question 6.*

The next questions refer to the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your Crohn's disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your Crohn's disease. Do not include time you missed to participate in this study.*

\_\_\_\_\_ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as annual leave, holidays, time off to participate in this study?

\_\_\_\_\_ HOURS

4. During the past seven days, how many hours did you actually work?

\_\_\_\_\_ HOURS *(If "0", skip to question 6)*



5. During the past seven days, how much did your Crohn's disease affect your productivity while you were working?

*Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If Crohn's disease affected your work only a little, choose a low number. Choose a high number if Crohn's disease affected your work a great deal.*

Crohn's disease had no effect on my work	<div style="display: flex; justify-content: space-around; width: 100%;"> <span>0</span><span>1</span><span>2</span><span>3</span><span>4</span><span>5</span><span>6</span><span>7</span><span>8</span><span>9</span><span>10</span> </div>	Crohn's disease completely prevented me from working
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CIRCLE A NUMBER

6. During the past seven days, how much did your Crohn's disease affect your ability to perform your normal daily activities, excluding your job?

*By normal activities, we mean the usual activities you perform, such as working around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could perform and times you accomplished less than you would like. If Crohn's disease affected your activities only a little, choose a low number. Choose a high number if Crohn's disease affected your activities a great deal.*

Crohn's disease had no effect on my daily activities	<div style="display: flex; justify-content: space-around; width: 100%;"> <span>0</span><span>1</span><span>2</span><span>3</span><span>4</span><span>5</span><span>6</span><span>7</span><span>8</span><span>9</span><span>10</span> </div>	Crohn's disease completely prevented me from doing my daily activities
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CIRCLE A NUMBER

WPAI-CD (UK English)